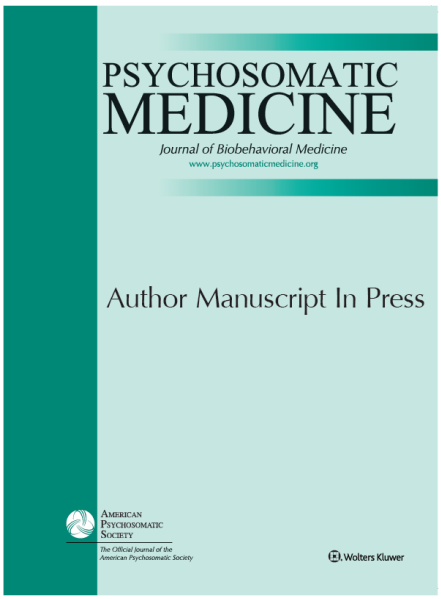
Longitudinal Associations Between Inflammation and Depressive Symptoms in Chronic Dialysis Patients

Haverkamp, Gertrud L. G.; Loosman, Wim L.; Schouten, Robbert W.; Franssen, Casper F. M.; Kema, Ido P.; van Diepen, Merel; Dekker, Friedo W.; Shaw, Prataap K. Chandie; Smets, Yves F. C.; Vleming, Louis-Jean

Published in:
Psychosomatic Medicine

DOI:
10.1097/PSY.0000000000000649



Psychosomatic Medicine
Author's Accepted Manuscript

Article Title: Longitudinal associations between inflammation and depressive symptoms in chronic dialysis patients

Authors: Gertrud L.G. Haverkamp, Wim L. Loosman, Robbert W. Schouten, Casper F.M. Franssen, Ido P. Kema, Merel van Diepen, Friedo W. Dekker, Prataap K. Chandie Shaw, Yves F.C. Smets, Louis-Jean Vleming, Brigit C. van Jaarsveld, Adriaan Honig, and Carl E. Siegert

DOI: 10.1097/PSY.0000000000000649

Received Date: November 27, 2017
Revised Date: June 27, 2018

Psychosomatic Medicine Publish Ahead of Print
DOI: 10.1097/PSY.0000000000000649

Longitudinal associations between inflammation and depressive symptoms in chronic dialysis patients

Gertrud L.G. Haverkamp, MD, PhD[1,2], Wim L. Loosman, MD, PhD[1,2], Robbert W. Schouten, MD[1,2], Casper F.M. Franssen, MD, PhD[3], Ido P. Kema, PhD[4], Merel van Diepen, PhD[5] , Friedo W. Dekker, MD, PhD[5], Prataap K. Chandie Shaw, MD, PhD[6], Yves F.C. Smets, MD, PhD[7], Louis-Jean Vleming, MD, PhD[8], Brigit C. van Jaarsveld, MD, PhD[9], Adriaan Honig, MD, PhD[2,10], Carl E. Siegert, MD, PhD[1]

[1] Department of Nephrology, OLVG west, Amsterdam, The Netherlands

[2] Department of Psychiatry, OLVG west, Amsterdam, The Netherlands

[3] Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[4] Department of Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[5] Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

[6] Department of Nephrology, Medical Center Haaglanden, The Hague, The Netherlands

[7] Department of Nephrology, OLVG east, Amsterdam, The Netherlands

[8] Department of Nephrology, Haga Hospital, The Hague, The Netherlands

[9] Department of Nephrology, VU Medical Center, Amsterdam, The Netherlands

[10] Department of Psychiatry, VU Medical Center, Amsterdam, The Netherlands

Corresponding author:

Gertrud L.G. Haverkamp

OLVG west, Department of Nephrology

Jan Tooropstraat 164, 1061AE Amsterdam, The Netherlands

Phone number: +31650646038

E-mail: g.haverkamp@olvg.nl

Conflicts of Interest and source of funding:

None declared.

This study was funded by the Dutch Kidney Foundation. The Dutch Kidney Foundation had no influence in study design whatsoever.

Abstract

Objective

Patients undergoing chronic dialysis often display sustained elevations of inflammation markers and also have a high prevalence of depressive symptoms. Although multiple studies demonstrated cross-sectional associations between inflammation markers and depressive symptoms in this patient group, longitudinal associations have not been examined. We therefore investigated whether longitudinal associations exist between inflammation markers and depressive symptoms in chronic dialysis patients.

Methods

Data of three consecutive measurements of an observational, prospective cohort study among chronic dialysis patients were used. At baseline, 6 months and 12 months follow-up, patients completed the Beck Depression Inventory (BDI) and inflammation markers (HsCRP, IL-1β, IL-6, IL-10, and TNFα) were measured. We examined cross-sectional associations between inflammation markers and depressive symptoms using linear regression models. The longitudinal association between inflammation and depressive symptoms was assessed using a linear mixed model analyses.

Results

A total of 513 patients were included. Cross-sectional associations were found between HsCRP and depressive symptoms at baseline (β= 0.9 (CI: 0.4-1.4)) and 6 months follow-up (β= 1.1 (CI: 0.3-2.0)), and between IL-1β and depressive symptoms at 6 months follow-up (β= 1.3 (CI: 0.8-

1.8)) and 12 months follow-up (β= 1.2 (CI: 0.4-1.9)). Inflammation makers (HsCRP, IL-6, IL-1β, IL-10 and TNFa) at baseline were not associated with depressive symptoms at follow-up and vice versa.

Conclusion

We confirmed the presence of cross-sectional associations between inflammation markers and depressive symptoms in chronic dialysis patients, but with our longitudinal data we found no longitudinal associations. This supports an associative instead of a causal relationship between inflammation and depressive symptoms.

Keywords:

chronic dialysis patients; depressive symptoms; inflammation markers; longitudinal associations

Acronyms:

BDI= Beck Depression Inventory; BMI= Body Mass Index; GFR= Glomerular Filtration Rate; HsCRP= High sensitivity C-reactive protein; HPA-axis= Hypothalamic-Pituitary-Adrenal-axis; IL= Interleukine; IDO= indoleamine-2,3-dioxygenase; M0= Measurement at baseline; M6= Measurement at 6 months follow-up; M12= Measurement at 12 months follow-up; TNFα= Tumor necrosis factor α; 5-HT= Serotonine.

Introduction

Chronic dialysis patients are known for the presence of a chronic inflammatory state[1] and for a high prevalence of depressive symptoms[2]. Depressive symptoms are associated with morbidity and both short-term and long-term mortality in dialysis patients[3-6]. Also higher levels of inflammation markers (especially CRP) have been found to be associated with both higher morbidity and mortality[7-10]. Multiple studies have examined cross-sectional associations between high levels of inflammation markers and depressive symptoms in dialysis patients[11]. A recent systematic review demonstrated a mixed outcome of these studies: with some studies demonstrating significant cross-sectional associations, while other studies failed to[11]. Besides, effect sizes in previous studies are mostly small and the existence of an association is still uncertain[11;12]. Long term associations between inflammation markers and depressive symptoms and especially the direction of this association have to the best of our knowledge not been examined in chronic dialysis patients.

The direction of the relationship between inflammation and depression has been studied in the general population[13-17]. Some studies demonstrated that depression may lead to subsequent inflammation[13;14;17], whereas other studies have found that inflammation may precede depression[18-21]. One study found evidence for a bidirectional relationship over a 1 to 2 year follow-up period[16]. On the basis of these results the cause-effect relationship between inflammation and depression could run in either direction.

The exact mechanism explaining the link between inflammation and depressive symptoms is not clear[22]. Theories have been formulated to explain both directionalities. On the one

hand, inflammation could cause subsequent depression via activation of the enzyme indoleamine-2,3-dioxygenase (IDO), which degrades tryptophan (the precursor of serotonin) into kynurenine leading to low serotonin levels[23]. It is known that lower concentrations of serotonin in the central nervous system may cause depressive symptoms[24]. This theory is especially plausible in the dialysis population as these patients are not only known for high levels of inflammation, but also for low tryptophan levels and high kynurenine levels[25;26]. Also, the degradation products of tryptophan might play a role, as these degradation products lead to oxidative stress and impair the mitochondrial metabolism and trigger apoptosis[27]. Inflammation could also cause depression via hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA)-axis[28]. On the other hand, depression may cause inflammation by reducing the sensitivity of the immune system to glucocorticoids responsible for terminating the inflammatory response[29;30]. Furthermore, clinical depression has also been linked to diminished activation of the parasympathetic nervous system, while activation of the parasympathetic system may also inhibit inflammation[17].

As the inflammatory state of dialysis patients is more pronounced than that of healthy individuals[31], it is uncertain whether results found in the general population can be extrapolated to the dialysis population. Therefore, the aim of this study is to examine whether longitudinal associations exist between inflammation markers and depressive symptoms in chronic dialysis patients. The second aim is to examine the directionality of the inflammation-depression association among chronic dialysis patients. We hypothesized that based on the theories described above, also in the dialysis population a bidirectional relationship between inflammation and depression may be found.

Methods

Study design

Data from the DIVERS study (Depression related factors In dialysis patients with Various Ethnicities and Races Study) were used. DIVERS is an observational, prospective cohort study of chronic dialysis patients in four urban teaching hospitals and one university hospital in The Netherlands.

Both prevalent and incident dialysis patients were included. Inclusion started in June 2012 and ended in December 2013 for prevalent patients. For incident patients the inclusion ended in December 2016. Included patients were assessed biannually until death, kidney transplantation, a transfer to a non-participating center, or discontinuation of participation because of motivational reasons.

Inclusion criteria were: ≥18 years of age, undergoing dialysis treatment (hemodialysis or peritoneal dialysis) for at least 90 days, and being able to complete a questionnaire in Dutch, English, Turkish or Moroccan Arabic. Patients with cognitive impairments (e.g. dementia) were excluded.

For the current study we used the measurements at baseline (M0), 6 months (M6) and 12 months (M12) follow-up until December 2014. At each time point patients completed a questionnaire and a blood sample was drawn. For hemodialysis patients the blood sample was taken immediately prior to a dialysis session and for peritoneal dialysis patients at an outpatient visit.

The DIVERS study was approved by the medical ethics committee of the VU University Medical Center (approval number: 2010/064). All patients gave their written informed consent prior to study inclusion.

Depressive symptoms

Depressive symptoms were assessed at baseline, 6 months and 12 months follow-up with the Beck Depression Inventory-II (BDI)[32;33]. The BDI is a 21-item self-report scale, with items scored on a scale of 0 to 3. Summed scores range from 0 to 63 and higher scores indicate more severe depressive symptoms. The BDI has been validated in one of the participating centers of the DIVERS study[34]. This study found a cut-off point of 13 for the detection of depression, with a sensitivity of 0.75 and specificity of 0.90. The cut-off point was only used to estimate the prevalence of depressive symptoms in this patient group. In the regression analyses the continuous outcome was used. A distinction can be made in cognitive-affective and somatic symptom scores. The cognitive-affective symptom score was calculated by summing BDI-II items 1-14 (sadness, pessimism, past failure, loss of pleasure, guilty feelings, punishment feelings, self-dislike, selfcriticalness, suicidal ideation, crying, agitation, loss of interest, indecisiveness, worthlessness). The somatic symptom score was calculated by summing BDI-II items 15-21 (loss of energy, sleep problems, irritability, appetite problems, concentration, fatigue, loss of interest in sex)[35;36].

Inflammation markers

Inflammation markers were assessed at baseline, 6 months and 12 months follow-up (single measurement). Peripheral blood was collected before dialysis and all samples were immediately

centrifuged. Serum aliquots were stored at -80 ºC until analysis. Baseline and follow-up serum samples were analyzed at the same time at the Department of Rheumatology & Clinical Immunology (University Medical Center Groningen, The Netherlands). Several pro-inflammation cytokines (HsCRP, IL-1β, IL-6, and TNFα) and the anti-inflammation cytokine (IL-10) were determined by using the Magnetic Luminex Screening or Performance assay (R&D Systems, Abingdon, UK) according to the manufacturer's instructions. Samples were measured using Luminex 100 System (Luminex, Austin, Tx, USA) and data were analyzed with StarStation software, version 2.3 (Applied Cytometry, Birmingham, UK).

The detection range for HsCRP after dilution (1000x) is 0.116-28.244ug/mL. The detection range for the other inflammation markers after dilution (2x) is for IL-1β 0.67-2800pg/mL, for IL-6 1.90-7800pg/mL, for IL-10 0.92-3800pg/mL and for TNF-α 1.52-6200pg/mL. The intra-assay coefficient of variation for HsCRP, IL-1β, IL-6, IL-10 and TNF- α is respectively 6.4, 5.3, 5.2, 5.4 and 5.3 and the inter-assay coefficient of variation is respectively 10.0, 12.8, 9.6, 10.8 and 9.6.

Covariates

At baseline the following socio-demographic characteristics were collected: partnership/marital status (yes/no), having children (yes/no), educational level (low versus average/high), race (White, Asian, or Black), current smoking (yes/no), and current alcohol use (yes/no). From electronic medical records were collected: age, sex, dialysis modality (hemodialysis or peritoneal dialysis), dialysis vintage, Body Mass Index (BMI, weight/height^2), primary kidney disease, comorbidities, anti-depressant use (yes/no), and residual diuresis . Dialysis vintage was deter-

mined in months on dialysis and a subdivision was made in incident (less than 6 months on dialysis) and prevalent patients (dialysis longer than 6 months). Primary kidney disease was classified according to the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) codes[37] and divided into 4 groups (diabetes mellitus, glomerulonephritis, renal vascular disease, and other). The Davies comorbidity index[38], was used to classify comorbidities in no, intermediate or severe comorbidity. Residual diuresis indicating remaining glomerular filtration rate (GFR), was defined as a urine production of >100 mL per day.

Statistical analysis

Participants were included if they had both a serum cytokine measurement and BDI score at one or more measurements (baseline or follow-up).

Standard descriptive statistics were used to present baseline characteristics. To examine the internal consistency of the BDI we calculated crohnbach's alpha for the BDI at all three time points on the non-imputed dataset. HsCRP, IL-1β, IL-6, and IL-10 were log transformed (natural logarithm) to normalize the distribution of the data. The change in inflammation markers and depressive symptom scores between time points was calculated by subtracting the mean values of the inflammation markers at M0 from M6, M0 from M12 and M6 from M12. All models were adjusted for the following confounders (collected at baseline): age, sex, education, race, smoking, alcohol use, BMI, dialysis modality, primary cause of renal failure, comorbidities, residual diuresis, and dialysis vintage.

First, cross-sectional associations were examined between inflammation markers and depressive symptoms at M0, M6 and M12 by using univariate and multivariate linear regression analysis. Second, the longitudinal relationship between inflammation and depressive symptoms was assessed by using a linear mixed model. This method makes optimal use of the available data during follow-up, accounts for correlations in the repeated measures in one subject over time, and appropriately handles missing data. Again both directions between inflammation and depressive symptoms were analyzed and all time points were used. The mixed models were fitted with a random intercept for participant and a repeated time effect. Models included the determinant under study, time, and the interaction between the determinant under study and time as fixed effects. Compound symmetry was used as the covariance structure.

Due to the log transformation of HsCRP, IL-1β, Il-6 and IL-10, the beta has to be interpreted at a different scale. Beta indicates differences in depressive symptoms related to 1 unit change in baseline log cytokine. Log (HsCRP) ranges from -7.87 to 4.83, log (IL-1β) from -11.17 to 3.20, log (IL-10) from -9.02 to 4.83, log (IL-6) from -6.93 to 4.36, and BDI from 0 to 56.

To perform the analysis on complete datasets we imputed missing data with multiple imputation techniques (10 repetitions) in SPSS. With multiple imputation missing data are imputed by a value that is predicted using all other available patient characteristics[39]. We imputed missing socio-demographic and clinical data and missing values on the BDI and cytokines. We performed both the linear regression analysis and linear mixed model on the imputed dataset.

Sensitivity analyses

We performed sensitivity analyses to test the robustness of our data. First, we assessed the longitudinal relationship between inflammation and depressive symptoms in patients with complete data on all three measurements for both cytokines and BDI score. Second, we also performed the analysis in the total patient group, without exclusion of patients who did not have a cytokine and depressive symptoms measurement at at least one time point. Third, we made a subdivision in incident and prevalent patients and performed the linear mixed model in both groups. We also performed the linear mixed model separately for patients with and without diabetes mellitus and for hemodialysis and peritoneal dialysis patients. We also performed the linear mixed model with the cognitive-affective and somatic symptom score as outcome and as predictor. Fourth, we examined the longitudinal association between inflammation markers and depressive symptoms by using linear regression models. Namely, (a) the association between baseline inflammation and depressive symptoms at 6 or 12 months follow-up was modeled, adjusted for depressive symptoms at baseline, and (b) the association between baseline depressive symptoms and inflammation at 6 or 12 months follow-up was modeled, adjusted for inflammation markers at baseline. Fifth, using the linear mixed model, imputation is not necessary as the model appropriately handles missing data. We performed the linear mixed model on both our imputed and non-imputed dataset. Sixth, we also performed a linear regression analysis between change in inflammation marker between time points and change in depressive symptom score between time points (M0-M6, M0-M12 and M6-M12) for patients with complete data on the three measuring points. Finally, by using a multiple imputation set only unstandardized coefficients are reported. We transformed our variables (predictors and outcome) into standardized variables and performed both the linear regression model and linear mixed model using the standardized variables to be able to

calculate standardized regression coefficients.

Results

Patient sample

A total of 548 chronic dialysis patients were included in the DIVERS study until December 2014. For the present analysis we included 513 patients who had at least a serum cytokine measurement and BDI score at one time point. One hundred ninety seven patients (38%) had complete data on all three time points for both cytokines and BDI scores, 162 patients (32%) had complete data on two time points, and 154 patients (30%) had complete data on one time point. Crohnbach's alpha for the BDI was at all three time points 0.9.

Baseline characteristics of the study sample are shown in table 1 for both the full sample (513 patients) and the sample with complete data on all three time points (197 patients) . The average age of the full sample was 64 (±15) years of age and 61% were male. Eighty nine percent were treated with hemodialysis and 32% were incident dialysis patients. The median dialysis vintage was 18 months. The prevalence of depression was 44% and 10% of the patients were treated with anti-depressants. Table 2 shows the median or mean level of the inflammation markers on the different time points. Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A521, shows the change in inflammation markers and depressive symptom scores between the different time points.

Cross-sectional associations between inflammation markers and depressive symptoms

Table 3 shows cross-sectional associations between inflammation markers and depressive symp-

toms at baseline, 6 months follow-up, and 12 months follow-up. At baseline HsCRP was significantly associated with depressive symptoms (β= 0.9 (CI: 0.4-1.4)), this association remained similar after adjustment for confounders. At 6 months HsCRP (β= 1.1 (CI: 0.3-2.0)), and IL-1β (β= 1.3 (CI: 0.8-1.8)), were significantly associated with depressive symptoms. After adjustment the associations were still significant for HsCRP (β= 1.0 (CI: 0.3-1.7)) and for IL-1β (β= 0.9 (CI: 0.4-1.4)). At 12 months only IL-1β was significantly associated with depressive symptoms (β= 1.2 (CI: 0.4-1.9)), also after adjustment this association was significant (β= 0.8 (CI: 0.01-1.6)).

Longitudinal associations between inflammation markers and depressive symptoms

Table 4 presents the longitudinal association between inflammation markers and depressive symptoms. Baseline inflammation markers (HsCRP, IL-6, IL-1β, IL-10 and TNFa) were not significantly associated with depressive symptoms at follow-up. Baseline depressive symptoms were not significantly associated with inflammation markers (HsCRP, IL-6, IL-1β, IL-10 and TNFa) at follow-up.

Sensitivity analyses

In patients with complete data on all three measurements (N=197) we also found no significant longitudinal associations between inflammation markers and depressive symptoms (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/PSYMED/A522). Comparable results were found in the total patient group (N=548) (data not shown). When dividing the patient group in incident (N=164) and prevalent (N=349) patients, we found no significant longitudinal associations in both groups (data not shown). We found similar results for patients with (N=216) and without diabetes mellitus (N=297) (data not shown). When dividing hemodialysis

patients (N=458) from peritoneal dialysis patients (N=55) we found no significant longitudinal associations in both groups (data not shown). By dividing the BDI symptom score in a cognitive-affective symptom score and a somatic symptom score we did not find significant longitudinal associations either (data not shown).

Examining the longitudinal association by using linear regression analysis we also found comparable results. Baseline inflammation markers (HsCRP, IL-6, IL-1β, IL-10 and TNFa) were not associated with depressive symptoms at 6 months and 12 months follow-up, although baseline TNFa showed a trend towards a significant association with depressive symptoms at 6 months follow-up. Baseline depressive symptoms were not associated with inflammation markers (HsCRP, IL-6, IL-1β, IL-10 and TNFa) at 6 or 12 months follow-up.

Performing the linear mixed model on the not imputed dataset also showed comparable results. In Supplementary Table 3, Supplemental Digital Content 3, http://links.lww.com/PSYMED/A523, the association between change in inflammation marker and change in depressive symptom score between the time points is shown for patients with complete data. The change in the level of IL-10 is significantly associated with change in depressive symptoms between time point M6 and M12. For all other inflammation markers and time points no significant associations were found. Finally, in Supplementary Table 4, Supplemental Digital Content 4, http://links.lww.com/PSYMED/A524 and Supplementary Table 5, Supplemental Digital Content 5, http://links.lww.com/PSYMED/A525, standardized regression coefficients are shown for respectively the cross-sectional associations and the longitudinal associations between inflammation markers and depressive symptoms.

Discussion

To the best of our knowledge, this is the first study examining long-term associations between inflammation markers and depressive symptoms in chronic dialysis patients. Cross-sectional associations between inflammation markers and depressive symptoms were found, but with the present longitudinal data we found no longitudinal associations between inflammation markers and depressive symptoms. Therefore, the direction of the association between inflammation markers and depressive symptoms in chronic dialysis patients cannot be determined yet.

In this study, cross-sectional associations were found between inflammation markers and depressive symptoms at baseline, 6 months follow-up and 12 months follow-up. However, these associations differed per time point: a significant association between HsCRP and depressive symptoms was found at baseline and 6 months follow-up, while IL-1β was only significantly associated with depressive symptoms at 6 months follow-up and 12 months follow-up. These results may explain why studies among chronic dialysis patients found mixed results. In a review by Taraz et al[11] including 23 studies only 11 studies found significant associations between inflammation markers and depressive symptoms. In those studies most significant associations with depressive symptoms were found for IL-6 and CRP. The use of different methods for the assessment of depressive symptoms and the use of different techniques for the analysis of plasma cytokine levels could be reasons for the lack of uniformity in the results of these previous studies[40]. However, despite the use of the same method for the assessment of depressive symptoms and of the same analysis techniques in also the same patient population we found varying results at the different time points. Therefore, the association between inflammation markers and depressive symptoms in chronic dialysis patients appears to be unstable and cross-sectional ana-

lyses may therefore provide mixed results that may reflect the involvement of several mechanisms in the pathogenesis of depression in chronic dialysis patients.

Bidirectional longitudinal associations between inflammation markers and depressive symptoms were not found in this study. When comparing associations (standardized coefficients in Supplementary Table 5, Supplemental Digital Content 5, http://links.lww.com/PSYMED/A525) in both directions, the associations seem equally strong. Our results are in contrast with earlier longitudinal reports in the general population where significant longitudinal associations between inflammation and depression have been found. However, in these general population studies most regression coefficients were small, suggesting a rather small effect of inflammation on long-term depression and vice versa[22]. Also, varying associations have been found in both directions and possible explanations for this variance may be different study populations studied, with different ethnicities, age, and sex. Another explanation could be that increased inflammation is part of a biologically specific subtype of depression[41], and therefore, the longitudinal and cross-sectional associations are not always found. Furthermore, it is known that in chronic dialysis patients complaints of uremia overlap with somatic symptoms of depression, making it more difficult to measure depression. By using the BDI it is possible to separate the somatic symptoms of depression from cognitive-affective symptoms. However, when examining the association between inflammation markers with the cognitive-affective symptom score of the BDI we did not find significant longitudinal associations either. In chronic dialysis patients also continuously varying cytokine concentrations may play a role, due to both the activation of leukocytes in hemodialysis releasing cytokines and due to removal of cytokines by dialysis treatment [42]. Finally, the relationship between inflammation and depres-

sion in chronic dialysis patients seems to be more associative instead of causal.

This study has several strengths, including the multicenter design, the prospective collection of data on inflammation markers and depressive symptoms at three different time points (providing the opportunity to examine the depression-inflammation relationship in two directions) and the measurement of five different inflammation markers (HsCRP, IL-1β, IL-6, IL-10, and TNFa) in a large cohort of dialysis patients. The study also has some limitations. Firstly, cross-sectional inflammation-depression studies showed smaller effect sizes when depression was measured with self-report questionnaires instead of diagnosing major depression by performing a structured interview[43]. We measured the presence of depressive symptoms by using the self-reported BDI questionnaire. It cannot be excluded that longitudinal associations between inflammation and depression would be found if the diagnosis of depression was made by using a structured clinical interview. Secondly, part of our patients were lost to follow-up due to death, kidney transplantation, loss of motivation, or due to recent inclusion no repeated measurements were available yet. However, by using multiple imputation techniques we used all our available data to estimate the missing data. This results in the best estimations of study associations, with correctly estimated standard errors and confidence intervals[39]. Thirdly, we performed a single measurement of cytokines at each time point. Double measurements (optimally at 2 weeks apart)[44] would provide more reliable measurements and stronger associations due to more accurate estimates. However, most studies examining the link between inflammation and depression were based on a single measurement[17]. Fourth, because all patients already received dialysis treatment prior to the collection of the blood samples, we can only conclude that change in inflammatory response does not lead to change in depression scores over time or vice versa, but

not that the onset of inflammation leads to the onset of depressive symptoms. As we included both incident and prevalent patients we were able to distinguish between patients receiving dialysis treatment for a short time (dialysis vintage between 3-6 months) or a longer time, but in both groups we found no longitudinal associations. Finally, the time interval of 6 and 12 months may be too short to develop depressive symptoms due to inflammation or vice versa. However, a study in the general population found significant associations between baseline inflammation and depression at 6 and 12 months follow-up[18].

In conclusion, cross-sectional associations between inflammation markers and depressive symptoms were found corroborating previous studies. No indications were found for longitudinal associations between inflammation markers and depressive symptoms in this population of chronic dialysis patients. So, in spite of the presence of a known chronic inflammatory state among chronic dialysis patients, this does not appear to cause the onset of depressive symptoms in the long term (6-12 months follow-up). These results support an associative rather than a causative relationship between inflammation and depressive symptoms in chronic dialysis patients.

Acknowledgements

This study was funded by the Dutch Kidney Foundation. The Kidney Foundation had no influence in study design whatsoever. We thank the nurses and participating dialysis centres of the DIVERS study for collection and management of the data. We gratefully thank all patients who participated in the DIVERS study.

Reference List

1. Amore A, Coppo R. Immunological basis of inflammation in dialysis. Nephrol Dial Transplant 2002;17:16-24.
2. Palmer S, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, Pellegrini F, Saglimbene V, Logroscino G, Fishbane S, Strippoli GF. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney Int 2013;84:179-191.
3. Boulware LE, Liu Y, Fink NE, Coresh J, Ford DE, Klag MJ, Powe NR. Temporal relation among depression symptoms, cardiovascular disease events, and mortality in end-stage renal disease: contribution of reverse causality. Clin J Am Soc Nephrol 2006;1:496-504.
4. Kimmel PL, Peterson RA, Weihs KL, Simmens SJ, Alleyne S, Cruz I, Veis JH. Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. Kidney Int 2000;57:2093-2098.
5. Riezebos RK, Nauta KJ, Honig A, Dekker FW, Siegert CE. The association of depressive symptoms with survival in a Dutch cohort of patients with end-stage renal disease. Nephrol Dial Transplant 2010;25:231-236.
6. van Dijk S, van den Beukel TO, Dekker FW, le CS, Kaptein AA, Honig A, Siegert CE, Boeschoten EW, Krediet RT, Verduijn M. Short-term versus long-term effects of depressive symptoms on mortality in patients on dialysis. Psychosomatic Medicine 2012;74:854-860.
7. Bazeley J, Bieber B, Li Y, Morgenstern H, de SP, Combe C, Yamamoto H, Gallagher M,

Port FK, Robinson BM. C-reactive protein and prediction of 1-year mortality in prevalent hemodialysis patients. Clin J Am Soc Nephrol 2011;6:2452-2461.

8. Honda H, Qureshi AR, Heimburger O, Barany P, Wang K, Pecoits-Filho R, Stenvinkel P, Lindholm B. Serum albumin, C-reactive protein, interleukin 6, and fetuin a as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. Am J Kidney Dis 2006;47:139-148.
9. Kimmel PL, Phillips TM, Simmens SJ, Peterson RA, Weihs KL, Alleyne S, Cruz I, Yanovski JA, Veis JH. Immunologic function and survival in hemodialysis patients. Kidney Int 1998;54:236-244.
10. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 1999;55:648-658.
11. Taraz M, Taraz S, Dashti-Khavidaki S. Association between depression and inflammatory/anti-inflammatory cytokines in chronic kidney disease and end-stage renal disease patients: a review of literature. Hemodial Int 2015;19:11-22.
12. Chilcot J, Friedli K, Guirguis A, Wellsted D, Farrington K, Davenport A. C reactive protein and depressive symptoms in hemodialysis patients: A questionable association. Hemodial Int 2017;21:542-548.
13. Copeland WE, Shanahan L, Worthman C, Angold A, Costello EJ. Cumulative depression episodes predict later C-reactive protein levels: a prospective analysis. Biol Psychiatry 2012;71:15-21.
14. Deverts DJ, Cohen S, DiLillo VG, Lewis CE, Kiefe C, Whooley M, Matthews KA. Depressive symptoms, race, and circulating C-reactive protein: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Psychosom Med 2010;72:734-741.

15. Gimeno D, Kivimaki M, Brunner EJ, Elovainio M, De VR, Steptoe A, Kumari M, Lowe GD, Rumley A, Marmot MG, Ferrie JE. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychol Med 2009;39:413-423.
16. Matthews KA, Schott LL, Bromberger JT, Cyranowski JM, Everson-Rose SA, Sowers M. Are there bi-directional associations between depressive symptoms and C-reactive protein in mid-life women? Brain Behav Immun 2010;24:96-101.
17. Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression-inflammation relationship. Brain Behav Immun 2009;23:936-944.
18. Matheny ME, Miller RR, Shardell MD, Hawkes WG, Lenze EJ, Magaziner J, Orwig DL. Inflammatory cytokine levels and depressive symptoms in older women in the year after hip fracture: findings from the Baltimore Hip Studies. J Am Geriatr Soc 2011;59:2249-2255.
19. Milaneschi Y, Corsi AM, Penninx BW, Bandinelli S, Guralnik JM, Ferrucci L. Interleukin-1 receptor antagonist and incident depressive symptoms over 6 years in older persons: the InCHIANTI study. Biol Psychiatry 2009;65:973-978.
20. Pasco JA, Nicholson GC, Williams LJ, Jacka FN, Henry MJ, Kotowicz MA, Schneider HG, Leonard BE, Berk M. Association of high-sensitivity C-reactive protein with de novo major depression. Br J Psychiatry 2010;197:372-377.
21. van den Biggelaar AH, Gussekloo J, de Craen AJ, Frolich M, Stek ML, van der Mast RC, Westendorp RG. Inflammation and interleukin-1 signaling network contribute to depressive symptoms but not cognitive decline in old age. Exp Gerontol 2007;42:693-

701.

22. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J Affect Disord 2013;150:736-744.
23. Christmas DM, Potokar J, Davies SJ. A biological pathway linking inflammation and depression: activation of indoleamine 2,3-dioxygenase. Neuropsychiatr Dis Treat 2011;7:431-439.
24. Oxenkrug G. Serotonin-kynurenine hypothesis of depression: historical overview and recent developments. Curr Drug Targets 2013;14:514-521.
25. Koenig P, Nagl C, Neurauter G, Schennach H, Brandacher G, Fuchs D. Enhanced degradation of tryptophan in patients on hemodialysis. Clin Nephrol 2010;74:465-470.
26. Pawlak D, Pawlak K, Malyszko J, Mysliwiec M, Buczko W. Accumulation of toxic products degradation of kynurenine in hemodialyzed patients. Int Urol Nephrol 2001;33:399-404.
27. Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:702-721.
28. Jehn CF, Kuhnhardt D, Bartholomae A, Pfeiffer S, Schmid P, Possinger K, Flath BC, Luftner D. Association of IL-6, hypothalamus-pituitary-adrenal axis function, and depression in patients with cancer. Integr Cancer Ther 2010;9:270-275.
29. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. J Psychosom Res

2002;53:897-902.

30. Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. Health Psychol 2002;21:531-541.
31. Friedrich B, Alexander D, Janessa A, Haring HU, Lang F, Risler T. Acute effects of hemodialysis on cytokine transcription profiles: evidence for C-reactive protein-dependency of mediator induction. Kidney Int 2006;70:2124-2130.
32. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory- II. Psychological Corporation. 1996:
33. Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-571.
34. Loosman WL, Siegert CE, Korzec A, Honig A. Validity of the Hospital Anxiety and Depression Scale and the Beck Depression Inventory for use in end-stage renal disease patients. Br J Clin Psychol 2010;49:507-516.
35. Chilcot J, Norton S, Wellsted D, Almond M, Davenport A, Farrington K. A confirmatory factor analysis of the Beck Depression Inventory-II in end-stage renal disease patients. J Psychosom Res 2011;71:148-153.
36. Thombs BD, Ziegelstein RC, Pilote L, Dozois DJ, Beck AT, Dobson KS, Fuss S, de JP, Grace SL, Stewart DE, Ormel J, Abbey SE. Somatic symptom overlap in Beck Depression Inventory-II scores following myocardial infarction. Br J Psychiatry 2010;197:61-66.
37. van Dijk PC, Jager KJ, de Charro F, Collart F, Cornet R, Dekker FW, Gronhagen-Riska C, Kramar R, Leivestad T, Simpson K, Briggs JD. Renal replacement therapy in Europe:

the results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. Nephrol Dial Transplant 2001;16:1120-1129.

38. Davies SJ, Russell L, Bryan J, Phillips L, Russell GI. Comorbidity, urea kinetics, and appetite in continuous ambulatory peritoneal dialysis patients: their interrelationship and prediction of survival. Am J Kidney Dis 1995;26:353-361.
39. de Goeij MC, van Diepen M, Jager KJ, Tripepi G, Zoccali C, Dekker FW. Multiple imputation: dealing with missing data. Nephrol Dial Transplant 2013;28:2415-2420.
40. Sonikian M, Metaxaki P, Papavasileiou D, Boufidou F, Vlassopoulos D, Vlahakos D. Effects of Interleukin-6 on Depression risk in dialysis patients. Am J Nephrol 2010;31:303-308.
41. Raison CL, Miller AH. Is depression an inflammatory disorder? Curr Psychiatry Rep 2011;13:467-475.
42. Jacobs P, Glorieux G, Vanholder R. Interleukin/cytokine profiles in haemodialysis and in continuous peritoneal dialysis. Nephrol Dial Transplant 2004;19 Suppl 5:V41-V45.
43. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;71:171-186.
44. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, Fadl YY, Friedman S, Hong Y, Myers GL, Rifai N, Smith SC, Taubert K, Trascey RP, Vinicor F. Markers of inflammation and cardiovascular disease. Circulation 2003;107:499-511.

Table 1. Baseline characteristics of chronic dialysis patients		
	Full sample (513 patients)	**Complete sample (197 patients)**
Socio-demographic characteristics		
Age, mean (SD)	64 (15)	66 (14)
Sex, male %	61	59
Partnership, partner %	52	51
Children, yes %	78	75
Education, low %	58	61
Race		
Caucasian, %	55	65
Asian, %	14	9
Black, %	31	26
Smoking, yes %	19	22
Alcohol use, yes%	26	28
Clinical characteristics		
Dialysis modality, hemodialysis %	89	91
Incident, yes %	32	20
Months on dialysis, median (IQ)	18 (5-51)	26 (10-58)
Body mass index kg/m2, mean (SD)	27 (6)	27 (6)
Residual renal function %	67	60
Primary cause of renal failure %		
Diabetes Mellitus	24	24
Glomerulonephritis	11	11
Renal vascular disease	27	28

Other	38	37
Davies comorbidity %		
No	27	22
Intermediate	55	59
Severe	18	19
Anti-depressants, yes %	10	8
Prevalence depression, yes %	44	45

Abbreviations: SD (standard deviation), IQ (interquartile range)

Table 2. Inflammation markers and depressive symptoms at baseline, 6 months and 12 months follow-up			
	M0 (N=495)	**M6 (N=358)**	**M12 (N=286)**
HsCRP, mg/L, median (IQ)	2.5 (0.7-6.8)	5.4 (1.3-23.1)	2.6 (0.8-9.6)
IL-1β, pg/mL, median (IQ)	0.06 (0.01-0.41)	0.01 (0.01-0.34)	0.01 (0.01-0.01)
IL-6, pg/mL, median (IQ)	2.7 (1.5-4.8)	2.5 (1.5-4.5)	2.7 (1.7-5.3)
IL-10, pg/mL, median (IQ)	0.34 (0.13-0.65)	0.29 (0.07-0.54)	0.32 (0.1-0.7)
TNF-α, pg/mL, mean (SD)	21.4 (11.9)	19.7 (10)	25.1 (15)
BDI >13 (%)	44	43	41
BDI score, mean (SD)	13.1 (9.7)	12.8 (9.5)	12.6 (10.0)

Abbreviations: SD (standard deviation), IQ (interquartile range), BDI (Beck Depression Inventory), M0 (baseline), M6 (6 months follow-up), M12 (12 months follow-up)

Table 3. Cross-sectional associations between inflammation markers and depressive symptoms at baseline, 6 months and 12 months follow-up in 513 chronic dialysis patients

	M0		M6		M12	
	B (95% CI) Unadjusted	B (95% CI) Adjusted	B (95% CI) Unadjusted	B (95% CI) Adjusted	B (95% CI) Unadjusted	B (95% CI) Adjusted
HsCRP^{L}	0.9 (0.4-1.4)*	0.9 (0.4-1.5)*	1.1 (0.3-2.0)*	1.0 (0.3-1.7)*	0.2 (-0.8-1.3)	0.2 (-0.6-1.1)
IL6^{L}	1.0 (-0.1-2.1)	0.8 (-0.3-2.0)	0.8 (-0.8-2.5)	0.8 (-0.6-2.1)	0.5 (-1.2-2.2)	0.5 (-1.1-2.0)
IL1β^{L}	-0.1 (-0.5- 0.3)	-0.2 (-0.6-0.3)	1.3 (0.8-1.8)*	0.9 (0.4-1.4)*	1.2 (0.4-1.9)*	0.8 (0.01-1.6)*
IL10^{L}	-0.3 (-0.8- 0.3)	-0.2 (-0.7- 0.4)	0.7 (-0.4- 1.7)	0.6 (-0.2- 1.4)	-0.3 (-1.2- 0.7)	-0.02 (-0.8- 0.8)
TNFa	0.01 (-0.1- 0.1)	-0.01 (-0.1- 0.1)	-0.003 (-0.2- 0.2)	0.003 (-0.1- 0.1)	-0.1 (-0.2- 0.1)	-0.04 (-0.1- 0.1)

^{L}=Log transformed

Abbreviations: B= unstandardized coefficient

* $P \leq 0.05$

Adjusted for: age, sex, education, race, smoking, alcohol, BMI, dialysis modality, primary cause of renal failure, comorbidities, residual diuresis, and dialysis vintage.

Table 4. Linear mixed model in both directions between inflammation markers and depressive symptoms in 513 chronic dialysis patients			
Predictor	Outcome	B (95% CI) Adjusted only for depressive symptoms at baseline or inflammation marker at baseline	B (95% CI) Adjusted
HsCRP^{L} baseline	Depressive symptoms	-0.03 (-0.4- 0.4)	0.01 (-0.4-0.4)
IL6^{L} baseline	Depressive symptoms	-0.1 (-0.8- 0.6)	0.3 (-0.4-1.1)
IL1β^{L} baseline	Depressive symptoms	-0.2 (-0.5- 0.2)	-0.1 (-0.4- 0.2)
IL10^{L} baseline	Depressive symptoms	0.1 (-0.3- 0.5)	0.2 (-0.2- 0.6)
TNFa baseline	Depressive symptoms	-0.01 (-0.2- 0.1)	0.01 (-0.1- 0.1)
Depressive symptoms baseline	HsCRP^{L}	-0.002 (-0.01-0.01)	-0.002 (-0.01- 0.01)
Depressive symptoms baseline	IL6^{L}	-0.001 (-0.01- 0.01)	-0.002 (-0.01- 0.01)
Depressive symptoms baseline	IL1β^{L}	-0.002 (-0.02- 0.02)	-0.003 (-0.02-0.01)
Depressive symptoms baseline	IL10^{L}	0.001 (-0.01- 0.02)	0.0003 (-0.01- 0.01)
Depressive symptoms baseline	TNFa	-0.01 (-0.1- 0.04)	-0.02 (-0.1- 0.1)

^{L}=Log transformed

Abbreviations: B= unstandardized coefficient

* $P \leq 0.05$

Adjusted for: depressive symptoms/inflammation marker at baseline and age, sex, education, race, smoking, alcohol, BMI, dialysis modality, primary cause of renal failure, comorbidities, residual diuresis, and dialysis vintage.